Pharmacodynamics: actual data

How shall we dose antibiotics?

- time-dependent
- concentration-dependent

With the support of Wallonie-Bruxelles-International
from pharmacokinetics to pharmacodynamics...

Pharmacokinetics
conc vs time

Pharmacodynamics
conc vs effect

PK/PD
effect vs time
from pharmacokinetics to pharmacodynamics...

- $C_{\text{max}}$
- $\text{AUC} > \text{MIC}$
- $\text{Cmax} / \text{MIC}$
- $\text{AUC} / \text{MIC}$
- $t > \text{MIC}$
- Time $\sim$ conc $> \text{MIC}$
Available antibiotics can be divided in 3 groups:

- time-dependent (T > MIC)
- AUC/MIC-dependent
- both AUC/MIC and peak/MIC-dependent
1. **Antibiotics with time-dependent effects and no or little persistent effects**

<table>
<thead>
<tr>
<th>AB</th>
<th>PK/PD parameter</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta$-lactams</td>
<td>Time above MIC</td>
<td>Maximize the exposure time</td>
</tr>
</tbody>
</table>
How long should you stay above the MIC?

- cefotaxime
- neutropenic mice
- *K. pneumoniae*
- lung infection

Moderate infections: 40%  
Serious infections: 100%  

$R^2 = 94\%$
More experimental data with penicillins, cephalosporins and carbapenems ...

Fig. 7. Relationship between the change in log$_{10}$ CFU per thigh or lung for various pathogens following 24 h of therapy with different doses of penicillins (△), cephalosporins (○), and carbapenems (□).

- different pathogens
- same shape of dose response
- diff. in $T > MIC$ for a static effect (penicill. > carbap.)
- diff $E_{max}$ (penicill. < carbap.)

How to optimize $T > \text{MIC}$?

1. Increase the unitary dose?:

![Graph showing concentration over time with MIC and dose levels](image)

- Concentration
- Time (h)
- MIC
- $dosis = 1$
How to optimize $T > MIC$?

1. Increase the unitary dose?

But useless peak!!

gain...

dosis = 1

dosis = 2

Concentration

Time (h)

MIC
How to optimize $T > \text{MIC}$?

2. Increase the number of administrations?

Seems more logical…
β-lactams: applications...

- Respiratory tract infections (oral route)...
- Serious infections (intravenous route)
Optimizing dosage for amoxycillin

oral amoxycillin (MIC = 1 mg/l)

T > MIC (%)

4X/day
3X/day
2X/day
1X/day

T > MIC
40 - 60 %

individual dose

0 500 1000 1500 2000
Optimizing dosage for amoxycillin

Oral amoxycillin (MIC = 1 mg/l)

T > MIC (%)

4X/day
3X/day
2X/day
1X/day

Appropriate dose = 500 mg 3-4 X/d or 1000 mg 2 X/d
Optimizing dosage for cefuroxime

oral cefuroxime (MIC = 1 mg/l)

T > MIC (%)

0 125 250 375 500

4X/day 3X/day 2X/day 1X/day

T > MIC 40 - 60 %

individual dosis

UCL PK/PD Course
April 2011
Optimizing dosage for cefuroxime

oral cefuroxime (MIC = 1 mg/l)

Appropriate dose = 125 mg 4 X/d or 250 mg 3 X/d or 500 mg 2 X/d
Oral $\beta$-lactams and *S. pneumoniae*

An MIC of $\sim 2 \mu g/ml$ is the limit that you can cover in optimal conditions, i.e. with a 3 x / day administration and a total daily dosis of

- $3 \text{ g}$ for amoxicillin
- $1-1.5 \text{ g}$ for cefuroxime-axetil

**PK/PD breakpoint for oral $\beta$-lactams:**

$\text{MIC} < 2 \mu g/ml$
β-lactams: applications...

- Respiratory tract infections (oral route)...
- Serious infections (intravenous route)
Typical pharmacokinetics of an IV $\beta$-lactam

<table>
<thead>
<tr>
<th>time (hours)</th>
<th>serum concentration for</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5 g</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>12.5</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td>1.5</td>
</tr>
<tr>
<td>12</td>
<td>0.75</td>
</tr>
</tbody>
</table>

* Single administration unique; half-life 2h; $V_d = 0.2$ l/kg
### Typical pharmacokinetics of an IV β-lactam

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<td>6</td>
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<tr>
<td>12</td>
<td>0.75</td>
</tr>
</tbody>
</table>

* Single administration unique; half-life 2h; $V_d = 0.2$ l/kg

Where would you like to be?
Optimisation of IV $\beta$-lactams for "difficult" organisms

- 2 g every 12 h  \[ T > \text{MIC} = 100\% \]
  - if MIC $\leq$ 3 mg/L
- 2 g every 8 h  \[ T > \text{MIC} = 100\% \]
  - if MIC $\leq$ 12 mg/L

More frequent administrations is the best way to increase the activity of $\beta$-lactams in difficult-to-treat infections...

PK / PD breakpoint for IV $\beta$-lactams: MIC < 8 $\mu$g/ml
Can we do still better?

3. Continuous infusion

Concentration always above the MIC!
Continuous infusion: the solution?

Yes:

- Optimized mode of administration
- Possibility to obtain stable concentrations as high as 20 to 40 mg/L

But be careful …

- To the stability of the molecule
  - The β-lactam ring is intrinsically breakable …
  - Temperature !!!
- To incompatibilities with other molecules also administered by continuous infusion

Caution rules need to be respected ….
Continuous infusion: the solution?

Yes:

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But be careful…

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  - Temperature!!!
- To incompatibilities with other molecules also administered by continuous infusion

There will be a special course on β-lactams by continuous infusion!!

Caution rules need to be respected …. 
Antibiotics Group # 2  
(after W.A. Craig, 2000; revised 2002 and 2003)

2. Antibiotics with **time-dependent effects**, no or little influence of concentration, but marked persistent effects

<table>
<thead>
<tr>
<th>AB</th>
<th>PK/PD parameter</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>glycopeptides</td>
<td>AUC / MIC</td>
<td>optimize the amount of antibiotic</td>
</tr>
<tr>
<td>tetracyclines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>macrolides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>streptogramins</td>
<td></td>
<td></td>
</tr>
<tr>
<td>oxazolidinones</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3. Antibiotics with concentration-dependent bactericidal activity and prolonged persistent effects (post-antibiotic effects)

<table>
<thead>
<tr>
<th>AB</th>
<th>PK/PD parameter</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>aminoglycosides</td>
<td>Peak and AUC / MIC</td>
<td>optimize the peak and the amount of antibiotic</td>
</tr>
<tr>
<td>fluoroquinolones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>daptomycin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Aminoglycosides: get a peak!
Aminoglycosides: get a peak!

Peak/MIC > 8

1. Appropriate mode of administration
   - IV route

2. Calculation of the necessary peak value
   - minimal peak: $= \text{MIC} \times 8$

3. Calculation of the adequate dosage
   - peak $= \text{dosis} / \text{Vd}$
   - dosis $= \text{peak} \times \text{Vd}$
   - dosis $= \text{MIC} \times 8 \times \text{Vd}$
Aminoglycosides: get a peak!

3 mg / kg - 1 X day

MIC = 0.5 → peak/MIC ~ 24

MIC = 2 → peak/MIC ~ 6

* aminoglycoside with half-life= 1 h and  $V_d = 0.25$ l/kg
Aminoglycosides: get a peak!

Increase the dose!

* aminoglycoside with half-life = 1 h and $V_d = 0.25 \text{ l/kg}$

\begin{align*}
\text{MIC} = 0.5 & \rightarrow \text{peak/MIC} \sim 48 \\
\text{MIC} = 2 & \rightarrow \text{peak/MIC} \sim 12
\end{align*}

6 mg / kg - 1 X jour
Aminoglycosides: which dosis for which MIC?

<table>
<thead>
<tr>
<th>dose (mg/kg)</th>
<th>peak (mg/L) for $V_d = 0.25$ l/kg</th>
<th>peak/MIC if MIC =</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>1 2 4 8</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>2 4 8 16</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>3 6 12 24</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>4 8 16 32</td>
</tr>
<tr>
<td>6</td>
<td>24</td>
<td>6 12 24 48</td>
</tr>
<tr>
<td>8</td>
<td>32</td>
<td>8 16 32 64</td>
</tr>
</tbody>
</table>
### Aminoglycosides: which dosage for which MIC?

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Peak (mg/L) for $V_d = 0.25 \text{ l/kg}$</th>
<th>peak/MIC if MIC =</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>12</td>
<td>4 2 1 0.5</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>4 8 16 32</td>
</tr>
<tr>
<td>6</td>
<td>24</td>
<td>6 12 24 48</td>
</tr>
<tr>
<td>8</td>
<td>32</td>
<td>8 16 32 64</td>
</tr>
</tbody>
</table>

There will be a special course on aminoglycosides dose optimization!
Optimization of aminoglycoside usage

do not try to treat with aminoglycosides bacteria with MIC

- > 2 µg/ml for molecules with maximal daily dose of 6 mg/kg
- > 4 µg/ml for molecules with maximal daily dose of 15 mg/kg

PK / PD breakpoints for AG

- Genta, Netil, Tobra : 2 µg / ml
- Amika / Isépa : 4 µg / ml
Fluoroquinolones: get a peak and an AUC!

- Increase the amount administered, in order to optimize AUC/MIC, should be > 125.
- And peak/MIC, should be > 10.

Get both a peak and a AUC!!

MIC data: J. Verhaegen et al., 2001.
How to optimize the AUC / CMI ratio?

AUC = \text{dosis} / \text{Cl}

- Adjust the daily dose
  \sim \text{target AUC}

- Adapt the number of administrations
  \sim \text{pharmacokinetics of the drug}
AUC and peak after one dose are directly related to this dose.

A "theoretical" example...

- Concentration: 1 g, AUC = 24
- Concentration: 0.5 g, AUC = 12
- Concentration: 1 g, AUC = 5
- Concentration: 0.5 g, AUC = 2.5
24h-AUC is inversely related to the drug clearance (BUT so is NOT the peak …)

A “theoretical” example…

- AUC = 48
- AUC = 24
- AUC = 12

1g

\[ t^{\frac{1}{2}} = 2 \text{ h} \]

\[ t^{\frac{1}{2}} = 1 \text{ h} \]

\[ t^{\frac{1}{2}} = 0.5 \text{ h} \]

\( \approx 5 \)
24h-AUC is correlated to the number of unit doses (BUT, again, so is NOT the peak …)

A "theoretical" example...

\[ AUC = 48 \]

\[ AUC = 24 \]
PK/PD of fluoroquinolones in a nutshell

Remember:

- 24h-AUC is proportional to the daily dose
- peak is proportional to the unit dose...

- get a $\frac{24\text{h-AUC}}{\text{MIC}} > 125$, and
- get a peak / MIC ratio $> 8$

→ efficacy

- get this with the total daily dose and the appropriate unit dose ...
Patients respond to quinolones as a function of the 24 h-AUC of the quinolone they receive and the MIC of the offending organism (example for Gram - infections seen in the "Methods")

But remember that, for Gram (+), the immune status is critical ... (as seen in the methods)

Relationship Between 24 Hr AUC/MIC and Mortality for Fluoroquinolones against *S. pneumoniae* in Immunocompetent vs. Immunocompromised animal Models

Adapted from W.A. Craig: 7th ISAP Educational Workshop, San Diego, CA, 2002
## Defining PK/PD breakpoints for fluoroquinolones

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>PK/PD Bkpts (mg/L)</th>
<th>AUC/MIC (mg/24h)</th>
<th>peak / MIC (24h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>norfloxacin</td>
<td>800</td>
<td>0.1</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>500</td>
<td>0.1</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>ofloxacin</td>
<td>400</td>
<td>0.2-0.4</td>
<td>0.3 - 0.4</td>
<td></td>
</tr>
<tr>
<td>levofloxacin</td>
<td>500</td>
<td>0.4</td>
<td>0.4 - 0.5</td>
<td></td>
</tr>
<tr>
<td>moxifloxacin</td>
<td>400</td>
<td>0.4</td>
<td>0.4</td>
<td></td>
</tr>
</tbody>
</table>
Adjust the dose to the MIC

<table>
<thead>
<tr>
<th>Daily dosage of levofloxacin</th>
<th>AUC *</th>
<th>MIC for an AUC\textsubscript{24h}/MIC = 125</th>
</tr>
</thead>
<tbody>
<tr>
<td>250</td>
<td>28</td>
<td>0.2</td>
</tr>
<tr>
<td>500</td>
<td>56</td>
<td>0.4</td>
</tr>
<tr>
<td>1000</td>
<td>112</td>
<td>0.8</td>
</tr>
</tbody>
</table>

* based on normal half-lifes; CL ~ 100 mg/dl; doses for an adult of 65 kg
But keep the unitary dose in the allowed limit ... 

Peak-related side effects:

SNC toxicity

Inhibition of CYP 450 activity
chondrotoxicity
phototoxicity
Choose the most active molecule

<table>
<thead>
<tr>
<th>drug</th>
<th>Dosage (mg/24h)</th>
<th>AUC *</th>
<th>MIC for AUC/MIC = 125</th>
<th>MIC S. pneumo</th>
</tr>
</thead>
<tbody>
<tr>
<td>ofloxacin</td>
<td>400</td>
<td>66</td>
<td>0.5</td>
<td>2</td>
</tr>
<tr>
<td>levofloxacin</td>
<td>500</td>
<td>73</td>
<td>0.4</td>
<td>1</td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>1000</td>
<td>40</td>
<td>0.3</td>
<td>0.5-2</td>
</tr>
<tr>
<td>moxifloxacin</td>
<td>400</td>
<td>48</td>
<td>0.4</td>
<td>0.01-0.5</td>
</tr>
</tbody>
</table>

* AUC: Area Under the Curve
PK/PD: take home message

1. For each drug, choose on a **PK/PD basis** the appropriate
   - scheme of administration
   - daily dosage

2. Adapt the dosage to the **susceptibility** of the target organism,
   - based on MIC data for the individual patient
   - based on local epidemiology
PK/PD : from today to tomorrow

**today**: applying these concepts can help us to reach an optimized efficacy

**but let's prepare tomorrow:**

how can we use this science to avoid resistance development?

Section 4 A